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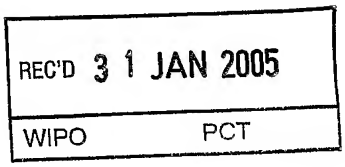

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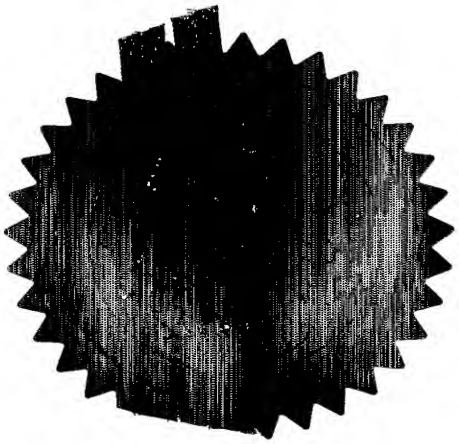

Signed Andrew Gersey

Dated 5 January 2005

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Patents Form 1/77

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The **Patent Office**

1/77

THE PATENT OFFICE
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31 DEC 2003
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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet, from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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South Wales NP10 8QQ

1. Your reference — JED1234

2. Patent application number *(The Patent Office will fill in this part)* — 0330206.4

31DEC03 E862681 4 D02806
P01/7700 0.00-0330206.4 CHEQ
UE

3 1 DEC 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Basant Kumar PURI
63 Caraway Road
Fulbourn
Cambridge
CB1 5DU

Patents ADP number *(if you know it)* 8781460001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — FORMATION CONTAINING A CARBOXYLIC ACID OR AN ESTER THEREOF

5. Name of your agent *(if you have one)* — Barker Brettell

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

St John's Innovation Centre
Cowley Road
Cambridge
CB4 OWS

Patents ADP number *(if you know it)* ~~7442494002~~ 7442496004

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of Filing *(day/month/year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier application	Date of filing *(day/month/year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? *Answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
Otherwise answer NO (See note(d)

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	13(x2)
Claim(s)	D L
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Barker Brettell — Date 30 December 2003

Barker Brettell

12. Name and daytime telephone number of person to contact in the United Kingdom — Toby Gosnall — Tel: 0121 456 1364

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b) Write your answers in capital letters using black ink or you may type them.
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FORMATION CONTAINING A CARBOXYLIC ACID OR AN ESTER THEREOF

This invention relates to a formulation comprising eicosapentaenoic acid, or an ester thereof, and a triterpene, or an ester thereof, and to its use in the treatment of, or manufacture of a medicament for the treatment of, a number of disorders. The formulation also has cosmetic uses. The invention also provides a method for the preparation of a formulation to be an orally administered or a method for the preparation of a formulation to be topically administered.

The present invention provides a formulation comprising:

(a) eicosapentaenoic acid or an ester thereof; and

(b) a triterpene or an ester thereof.

Eicosapentaenoic acid can be extracted in a natural form from the oil of fish, in particular from so called 'oily fish' such as sardines and salmon. Alternatively, eicosapentaenoic acid can be synthesised, for example ethyl eicosapentaenoic acid. Esters of eicosapentaenoic acid may be naturally occurring or synthesised. The formulation of the present invention may contain natural eicosapentaenoic acid, synthetic eicosapentaenoic acid, a naturally occurring ester of eicosapentaenoic acid or a synthetic ester of eicosapentaenoic acid, or a combination thereof.

Triterpenes refer to a family of naturally occurring compounds which may also be referred to as triterpenoids. The formulation of the invention may comprise a naturally occurring triterpene, a synthetic triterpene, a naturally occurring ester of a triterpene or a synthetic ester of a triterpene, or a combination thereof. Preferably the triterpene is a 3-*O*-trans caffeoyl derivative of betulinic acid, morolic acid or oleanolic acid,

faradiol-*O*-laurate, faradiol-*O*-palmitate or faradiol-*O*-myristate. Naturally occurring triterpenes can be isolated from a variety of plants including the flower heads of marigolds (*Calendula officinalis*), *Zygophyllum eichwaldii, Carthamus lanatus, Oenothera biennis* or *Pyrus comminus*.

The formulation may comprise up to 99% w/w of eicosapentaenoic acid or an ester thereof. Alternatively the formulation may comprise up to 99% w/w of triterpene or an ester thereof. The formulation may comprise up to 50% w/w of eicosapentaenoic acid or an ester thereof. The formulation may comprise up to 50% w/w of triterpene or an ester thereof. The formulation may comprise up to 70% w/w of eicosapentaenoic acid or an ester thereof, more preferably of 20 to 40% w/w, and 1 to 30% w/w of a triterpene or an ester thereof.

The amount of eicosapentaenoic acid or synthetic ester thereof, and triterpene or synthetic ester thereof, required to achieve the desired therapeutic or cosmetic effect will, of course, vary depending of the compounds used, the route of administration and the disorder or condition to be treated.

Preferably the formulation comprises eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof in a pharmaceutically acceptable form.

The formulation may also comprise a pharmaceutical carrier, diluent or excipient.

The formulation may also comprise one or more of a lubricant, a flavouring, a taste masking agent, a fragrance and a preservative.

Formulations containing eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, may also include other compounds for co-administration. Such compounds may include gamma-linolenic acid and docosahexaenoic acid

The formulation comprising eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, may be used to treat a variety of physiological and disease states including rheumatoid arthritis, osteoarthritis, back-ache, psoriasis, pre-menstrual syndrome, bacterial infections, diabetes mellitus, alcoholism, cancer, neurological disorders such as multiple sclerosis, epilepsy, tardive dyskinesia and choreiform disorders such as Huntington's disease, psychiatric disorders such as depression and attention-deficit/hyperactivity disorder, cardiovascular disorders such as hyperlipidemia and high blood pressure, dermatological disorders such as eczema and atopic dermatitis, respiratory disorders, learning disabilities and ageing.

The formulation comprising eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, may be administered orally.

The formulation may be administered orally as a liquid, a paste, a tablet or a capsule.

The oral formulation may be prepared as an inert porous matrix tablet which is obtained by mixing the eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, with waxes or water insoluble polymers and with fillers and binders. Paraffin, polyvinylchloride, ethylcellulose, stearylic alcohol, cetylic alcohol, carnauba wax, polyethylene, polyvinyl acetate, polymethyl methacrylate could be used as suitable diffusion retarding compounds. Other excipients used in the preparations of such tablets may include lactose, mannitol, calcium

phosphates, magnesium stearate, hydroxypropyl methylcellulose, methyl cellulose, polyvinylpyrrolidone, aluminium silicate, sodium carbonate, potassium phosphate or other suitable materials.

Alternatively, the formulation comprising eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, may be administered topically. The formulation to be applied topically may also comprise an occlusive agent, a surfactant system and water.

One or more various solvents that may be present in the topical formulation comprise various short chain alcohols including, but not limited to, ethyl alcohol, propylene alcohol, Triacetin, hexylen glycol and combinations thereof. The solvent may be present in an amount ranging from about 5.0 to about 30.0 w/w %.

Suitable occlusive agents that may be present in the topical formulation include, but are not limited to, petrolatum, microcrystalline wax, dimethicone, beeswax, mineral oil, squalane, liquid paraffin, shea butter, carnauba wax, SEPIGELO (a blend ofisoparaffin/polyacrylamide/laureth-7), and combinations thereof. The occlusive agent may be present in an amount of at least about 10.1 w/w %.

Suitable surfactant systems comprise at least one surfactant and exhibits a HLB value in a range from about 7.0 to about 10.9. The surfactant system may be present in the formulation in an amount ranging from about 0.25 to about 10.0 w/w%. Suitable surfactants include, but are not limited to, CETOMACROGOLO 1000, (Crodor, Inc.) glycerol monostearate, glycerol distearate, glyceryl stearate, polyoxyethylene stearate, a blend of glyceryl stearate and PEG-100 stearate (as ARLACEL 165), polysorbate 40, polysorbate 60, polysorbate 80,CETETH-200,

sorbitan monopalimate, sorbitan monostearate, sorbitan monooleate, and combinations thereof.

The topical formulation may also include a carrier, a skin conditioner, a preservative, a buffer, a fragrance, water or combinations thereof.

Accordingly to another aspect the invention provides a method for the treatment of various physiological and disease states including rheumatoid arthritis, osteoarthritis, back-ache, psoriasis, pre-menstrual syndrome, bacterial infections, diabetes mellitus, alcoholism, cancer, neurological disorders such as multiple sclerosis, epilepsy, tardive dyskinesia and choreiform disorders such as Huntington's disease, psychiatric disorders such as depression and attention-deficit/hyperactivity disorder, cardiovascular disorders such as hyperlipidemia and high blood pressure, dermatological disorders such as eczema and atopic dermatitis, respiratory disorders, learning disability and ageing, in a subject comprising administering to the subject an effective amount of a formulation comprising eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof.

According to a further aspect the invention provides a formulation comprising eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof for use in a method of treatment of a human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

In a further aspect the invention provides the use of eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, in the manufacture or preparation of a medicament for the treatment of various physiological and disease states including rheumatoid arthritis, osteoarthritis, back-ache, psoriasis, pre-menstrual syndrome, bacterial

infections, diabetes mellitus, alcoholism, cancer, neurological disorders such as multiple sclerosis, epilepsy, tardive dyskinesia and choreiform disorders such as Huntington's disease, psychiatric disorders such as depression and attention-deficit/hyperactivity disorder, cardiovascular disorders such as hyperlipidemia and high blood pressure, dermatological disorders such as eczema and atopic dermatitis, respiratory disorders, learning disabilities and ageing.

Formulations containing eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, may be used in cosmetic treatments. The cosmetic treatment may have an anti-ageing effect or to reverse the process of ageing.

Preferably the formulation comprises eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof in a cosmetically acceptable form.

The cosmetically acceptable formulation may also comprise a cosmetic carrier, diluent or excipient.

According to a yet further aspect the invention provides a method of cosmetic treatment comprising administering an effective amount of a formulation comprising eicosapentaenoic acid or an synthetic ester thereof, and a triterpene or an ester thereof.

Preferably, the formulation is administered as an anti-ageing formulation or to reverse the ageing process.

The cosmetic formulation may be administered orally or topically.

A yet further aspect of the invention provides a method for preparing a topical formulation comprising mixing eicosapentaenoic acid or an ester thereof and a triterpene or an ester thereof with a topically acceptable carrier.

The method may also comprise mixing the eicosapentaenoic acid or an ester thereof and the triterpene or an ester thereof with one or more of the following a solvent, an occlusive agent, a surfactant system and water.

The method may also comprise mixing the eicosapentaenoic acid or an ester thereof and the triterpene or an ester thereof with one or more of vitamin E (natural or an analogue), an emulsifying wax, honey, water, fragrance, an emulsifier and a mixture of ethyl, propyl and butyl parabens.

A still further aspect of the invention provides a method for preparing an orally administered formulation comprising mixing eicosapentaenoic acid or an ester thereof and a triterpene or an ester thereof with an orally acceptable carrier.

The method may also include mixing vitamin E (natural or an analogue) into the formulation. Vitamin E is an antioxidant and thus prevents unwanted oxidation.

The method may also include adding a flavouring or a taste masking agent to the formulation.

It will be appreciated that the compounds of eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, may be administered simultaneously, either in the same or different formulations, or sequentially. When there is sequential administration, the delay in

administering the second and any subsequent active ingredient should not be such as to lose the beneficial therapeutic or cosmetic effect of the combination. In a preferred aspect of the invention the eicosapentaenoic acid or an ester thereof, and the triterpene or an ester thereof, are administered in a combined formulation.

According to a further aspect the invention provides a method for the treatment of various physiological and disease states including rheumatoid arthritis, osteoarthritis, back-ache, psoriasis, pre-menstrual syndrome, bacterial infections, diabetes mellitus, alcoholism, cancer, neurological disorders such as multiple sclerosis, epilepsy, tardive dyskinesia and choreiform disorders such as Huntington's disease, psychiatric disorders such as depression and attention-deficit/hyperactivity disorder, cardiovascular disorders such as hyperlipidemia and high blood pressure, dermatological disorders such as eczema and atopic dermatitis, respiratory disorders, learning disabilities and ageing, in a subject comprising administering to the subject an effective amount of eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, wherein the eicosapentaenoic acid, or an ester thereof, and the triterpene, or an ester thereof, are administered simultaneously, either in the same or different formulations, or sequentially.

According to a yet further aspect the invention provides the use of eicosapentaenoic acid or an ester thereof, and a triterpene or an ester thereof, administered simultaneously, either in the same or different formulations, or sequentially, in a method of treatment of a human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

The present invention will now be illustrated, merely by way of example, with reference to the following methods and examples.

Method of extracting eicosapentaenoic acid and triterpenes

A method of extracting eicosapentaenoic acid from fish oil is described in Enzyme Microb Technol. 2000 Apr 1;26(7):516-529.

A method of extracting triterpenes from marigolds is described in Fitoterapia. 2003 Jun; 74(4):328-38. More specifically this paper discloses a method for the purification of the triterpenoid esters faradiol 3-*O*-laurate, palmitate and myristate from the flower heads of the medicinal plant *Calendula officinalis* (marigold).

Method of preparing a cream formulation for topical administration

A method for the preparation of a cream for topical application comprising eicosapentaenoic acid and a triterpene comprises placing the following components in a receptacle at room temperature:

- 122 g pure eicosapentaenoic acid;
- 20 g pure gamma-linolenic acid;
- 65 g organic, virgin, cold-pressed, non-raffinated evening primrose oil (which provides the triterpene);
- 3.4 g D alpha tocopheryl acetate;
- 180 g emulsifying wax; and
- 48 g clear honey.

The components are stirred together and then heated for one minute.

To this mixture is then added:

- 540 g water;

- 1.5 g fragrance (e.g. citrus: lime or lemon);
- 12 g of an emulsifier (to form a stable emulsion); and
- 30 g of a mixture of ethyl, propyl and butyl parabens.

The whole mixture is then gently stirred and heated for a further four minutes. It is then stirred slowly for a further five minutes until it has the required consistency for the cream. It is then transferred into glass jars that have been sterilized (at over 100 degrees C) using implements that have also been sterilized. Finally, lids that have also been sterilized are fastened on to the jars, which are then left to cool.

Method of preparing a formulation for oral administration

A method for the preparation of a formulation for oral administration containing eicosapentaenoic acid or a synthetic ester thereof, and a triterpene or a synthetic ester thereof, comprises placing the following components in a mixing bowl and manually mixing together for five minutes:

- pure eicosapentaenoic acid;
- pure gamma-linolenic acid;
- organic, virgin, cold-pressed, non-raffinated evening primrose oil; and
- D alpha tocopheryl acetate;

in a ratio, by mass, of 186 to 20 to 50 to 3.2.

Case studies on the use of a cream made according to the above described method

A number of studies have been undertaken to demonstrate the therapeutic and cosmetic effects of the cream made by the above-described method.

More specifically:

Cosmetic effect - Anti-ageing

Four subjects have thus far specifically used the cream made by the above-described method for its anti-ageing properties.

- Subject 1 - A female, aged 50, used the cream topically on her face and observed that within one week her skin looked younger and 'healthier, fresher, with a radiant look'. She described the cream as being far better than anything she has ever bought (e.g. evening primrose cream). She had sensitive skin, and noticed no adverse side-effects at all.
- Subject 2 – a female, aged 20, used the cream topically on her face, she also had sensitive skin, and again noticed within one week no adverse side-effects at all. She described her skin as looking healthier.
- Subject 3 – a female, aged 51, used the cream topically on her face, this subject derived similar benefits to subject 1, and described the result as being similar to 'botox without needles'.
- Subject 4 – a male aged 52, used the cream topically on his face, the subject described the effects within one week as being 'like a face-lift without surgery'.

All four subjects asked to continue applying the cream to their faces. The female subjects wish to use it instead of a traditional cosmetic foundation application.

These initial test results demonstrate the anti-ageing cosmetic effect of a cream according to the present invention.

Therapeutic effect - Back-ache

A female subject aged 75 with previously intractable back-ache began to derive relief of her back pain after three days' topical application of a cream made by the above-described method.

Therapeutic Effect - Arthritis

- Subject 1 - A female aged 69 suffering from severe rheumatoid arthritis in her hands, which had not responded to traditional medical treatment, applied cream made by the above-described method to her hands and an improvement was seen within one week.
- Subject 2 - An 89-year-old female with severe osteoarthritis in the hands, which had never previously responded to any treatment, showed improvement after one week when applying cream, made by the above-described method, to her hands. The improvements observed included relief from the pain, for the first time, and a decrease in the size of tophi (swellings).

Therapeutic/Cosmetic effect - Skin sores

A 69-year-old female subject with severe rheumatoid arthritis (see above) also noticed that her skin sores on her hands were much better seven to eight days after beginning use of the cream made by the above-described method. They had previously failed to respond to medical treatment and had had to be bandaged.

Therapeutic effect - Psoriasis

- Subject 1 - A female aged 17 with severe intractable treatment-resistant psoriasis started to improve after two to three days following topical application of cream, made by the above-described method, to her arms and legs.
- Subject 2 - A female aged 31 with severe psoriasis affecting her upper limbs responded after six to seven days when applying the cream, made by the above-described method, to her upper limbs; she had previously tried a wide range of medical and 'alternative' treatments, to no avail.

Therapeutic/Cosmetic effect - Eczema

A 52-year-old female subject with severe eczema responded within one week to the topical application of cream, made by the above-described method, again where conventional medical treatment had previously failed.

Oral Administration – Learning Difficulties

An 11 year old boy with learning difficulties started taking 1.5 g daily of the oral formulation discussed above. Within four weeks he started to show signs of improvement according to his parents and teachers. This improvement was in several domains, including cognitive functioning, reading and understanding his school work. The improvement continued and he reached a new, higher, level of intellectual functioning after three months, which has continued to be sustained for 6 months.

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